CLAIMS

What is claimed:

1. A method of preventing bone metastases comprising administering to a subject afflicted with metastatic cancer a therapeutically effective amount of M-CSF antagonist thereby preventing bone loss associated with the metastatic cancer.

2. A method of treating a subject afflicted with a metastatic cancer to bone comprising administering to said subject a therapeutically effective amount of M-CSF antagonist thereby reducing the severity of bone loss associated with the metastatic cancer.

3. The method according to claims 1 or 2 wherein said subject is a mammal.

4. The method according to claim 3 wherein said mammal is human.

5. The method according to claim 4 wherein said antagonist inhibits the interaction between M-CSF and its receptor (M-CSFR).

6. The method according to claim 5 wherein said antagonist inhibits osteoclast proliferation and/or differentiation induced by tumor cells.

7. The method according to claim 5 wherein said M-CSF antagonist is selected from the group consisting of:

a) a polypeptide comprising an anti-M-CSF antibody;

b) a polypeptide comprising an anti-M-CSFR antibody thereof;

c) a soluble polypeptide comprising an M-CSF mutein or derivative thereof; or

d) a soluble polypeptide comprising an M-CSFR mutein or derivative thereof.

8. The method according to claim 7 wherein said M-CSF antagonist is an anti-M-CSF antibody.

9. The method according to claim 7 wherein said M-CSF antagonist is a polypeptide comprising an anti-M-CSFR antibody.

10. The method according to claim 7 wherein said M-CSF antagonist is a soluble polypeptide comprising an M-CSF mutein or derivative thereof.

11. The method according to claim 7 wherein said M-CSF antagonist is a soluble polypeptide comprising an M-CSFR mutein or derivative thereof.

12. The method according to claim 8 or 9 wherein said antibody is selected

from the group consisting of:

a) a polyclonal antibody;

b) a monoclonal antibody;

c) a humanized antibody;

d) a human antibody;

e) a chimeric antibody;

f) Fab, $F(ab')_2$ or F_v antibody fragment; and

g) a mutein of any one of a) to f).

13. The method according to claim 8 wherein the antibody binds to the same epitope as monoclonal antibody 5H4 (ATCC Accession No. HB10027).

14. The method according to claim 7 wherein the metastatic cancer is breast, lung, renal, multiple myeloma, thyroid, prostate, adenocarcinoma, blood cell malignancies, including leukemia and lymphoma; head and neck cancers; gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, pancreatic cancer, liver cancer; malignancies of the female genital tract, including ovarian carcinoma, uterine endometrial cancers and cervical cancer; bladder cancer; brain cancer, including neuroblastoma; sarcoma, osteosarcoma; and skin cancer, including malignant melanoma or squamous cell cancer.

15. The method according to claim 8 wherein the M-CSF antagonist is an antibody administered at a dose between about 0.01 mg/kg and about 100 mg/kg.

16. A non-murine antibody that binds to M-CSF for treating a subject afflicted with a metastatic cancer, wherein said antibody effectively reduces the severity of bone loss associated with the metastatic cancer.

17. A non-murine monoclonal antibody that specifically binds to the same epitope of M-CSF as monoclonal antibody 5H4.

18. A non-murine monoclonal antibody that competes with monoclonal antibody 5H4 for binding to M-CSF more than 75%.

19. A non-murine antibody that binds to M-CSFR for treating a subject afflicted with a metastatic cancer, wherein said antibody effectively reduces the severity of bone loss associated with the metastatic cancer.

20. The antibody according to claim 16 wherein said antibody is selected from the group consisting of:

a) a polyclonal antibody;

b) a monoclonal antibody;

c) a humanized antibody;

d) a human antibody;

e) a chimeric antibody;

f) Fab, $F(ab')_2$ or F_v antibody fragment; and

g) a mutein of any one of a) to f).

21. The antibody according to claim 20 wherein the antibody is specific to M-CSF.

22. The antibody according to claim 20 wherein the antibody is specific to M-CSFR.

23. The antibody according to claim 20 wherein said antibody is a fully human antibody.

24. The antibody according to claim 20 wherein said antibody is a humanized antibody.

25. A hybridoma that secretes an antibody according to claim 23.

26. The antibody according to claim 20 wherein the cancer is breast, lung, renal, multiple myeloma, thyroid, prostate, adenocarcinoma, blood cell malignancies, including leukemia and lymphoma; head and neck cancers; gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, pancreatic cancer, liver cancer; malignancies of the female genital tract, including ovarian carcinoma, uterine endometrial cancers and cervical cancer; bladder cancer; brain cancer, including neuroblastoma; sarcoma, osteosarcoma; and skin cancer, including malignant melanoma or squamous cell cancer.

27. A pharmaceutical composition comprising any one of the antibodies of claims 17 to 26, and a pharmaceutically suitable carrier, excipient or diluent.

28. A method of screening for an M-CSF antagonist comprising the steps of:

a) contacting metastatic tumor cell medium, osteoclasts and a

candidate antagonist;

b) detecting osteoclast formation, proliferation and/or differentiation; and

c) identifying said candidate antagonist as an M-CSF antagonist if a decrease in osteoclast formation, proliferation and/or differentiation is detected.

29. The method of claim 28 wherein said metastatic tumor cell medium includes tumor cells.

30. The method of claim 28 wherein said contacting step (a) occurs *in vivo*, said detecting step (b) comprises detecting size and/or number of bone metastases, and said candidate antagonist is identified as an M-CSF antagonist if a decrease in size and/or number of bone metastases is detected.

31. The method of claim 28 further comprising the step of determining if said candidate antagonist binds to M-CSF.

32. The method of claim 28 further comprising the step of determining if said candidate antagonist inhibits interaction between M-CSF and its receptor M-CSFR.

33. The method according to claim 28 wherein said candidate antagonist is selected from the group consisting of:

a) a polypeptide comprising an anti-M-CSF antibody;

b) a polypeptide comprising an anti-M-CSFR antibody thereof;

c) a soluble polypeptide comprising an M-CSF mutein or derivative thereof;

d) a soluble polypeptide comprising an M-CSFR mutein or derivative thereof;

e) a peptide; or

f) a small molecule.

34. The method according to claim 33 wherein said candidate antagonist is an M-CSF mutein.

35. The method according to claim 33 wherein said candidate antagonist is an M-CSFR mutein.

36. The method according to claim 33 wherein said candidate antagonist is

an anti-M-CSF antibody.

37. The method according to claim 33 wherein said candidate antagonist is an anti-M-CSFR antibody.

38. A method of identifying an M-CSF antagonist that can prevent or treat metastatic cancer to bone, comprising the steps of:

(a) detecting binding of a candidate antagonist to M-CSF; and

(b) assaying the ability of said candidate antagonist to prevent or treat metastatic cancer to bone *in vitro* or *in vivo*.

39. A method of identifying an M-CSF antagonist that can prevent or treat metastatic cancer to bone, comprising the steps of:

(a) detecting binding of a candidate antagonist to M-CSFR; and

(b) assaying the ability of said candidate antagonist to prevent or treat metastatic cancer to bone *in vitro* or *in vivo*.

40. A method of identifying an M-CSF antagonist that can prevent or treat metastatic cancer to bone, comprising the steps of:

(a) identifying a candidate antagonist that inhibits the interaction between M-CSF and M-CSFR; and

(b) assaying the ability of said candidate antagonist to prevent or treat metastatic cancer to bone *in vitro* or *in vivo*.

41. A method of preventing bone metastases and tumor growth comprising administering to a subject afflicted with metastatic cancer therapeutically effective amounts of M-CSF antagonist and a therapeutic agent, thereby preventing bone loss associated with the metastatic cancer and preventing tumor growth.

42. A method of treating a subject afflicted with a metastatic cancer comprising administering to said subject therapeutically effective amounts of M-CSF antagonist and a therapeutic agent, thereby reducing the severity of bone loss associated with the metastatic cancer and inhibiting tumor growth.

43. The method according to claims 41 or 42 wherein said subject is a mammal.

44. The method according to claim 43 wherein said mammal is human.

45. The method according to claim 44 wherein said antagonist inhibits the interaction between M-CSF and its receptor M-CSFR.

46. The method according to claim 41 wherein said antagonist inhibits osteoclast proliferation and/or differentiation induced by tumor cells.

47. The method according to claim 45 wherein said M-CSF antagonist is selected from the group consisting of:

a) a polypeptide comprising an anti-M-CSF antibody;

b) a polypeptide comprising an anti-M-CSFR antibody thereof;

c) a soluble polypeptide comprising an M-CSF mutein or derivative thereof; and

d) a soluble polypeptide comprising an M-CSFR mutein or derivative thereof.

48. The method according to claim 47 wherein said antibody is selected from the group consisting of:

a) a polyclonal antibody;

b) a monoclonal antibody;

c) a humanized antibody;

d) a human antibody;

e) a chimeric antibody;

f) Fab, $F(ab')_2$ or F_v antibody fragment; and

g) a mutein of any one of a) to f).

49. The methods according to claims 41 or 42 wherein the therapeutic agent is a bisphosphonates.

50. The method according to claim 49 wherein the bisphonate is zeledronate, pamidronate, clodronate, etidronate, tilundronate, alendronate, or ibandronate.

51. The methods according to claims 41 or 42 wherin the therapeutic agent is a chemotherapeutic agent.

52. The method according to claim 51 wherein the subject is precluded from receiving bisphophonate treatment.

53. The methods according to claims 41 or 42 wherein the M-CSF

antagonist is effective to reduce the dosage of therapeutic agent required to achieve a therapeutic effect.

54. The methods according to claims 41 or 42 further comprising the step of administering a non-M-CSF colony stimulating factor, for example G-CSF.

55. A pharmaceutical composition comprising a M-CSF antagonist and a cancer therapeutic agent.

56. A package, vial or container comprising a medicament comprising an M-CSF antagonist and instructions that the medicament should be used in combination with surgery or radiation therapy.

57. A method of preventing or treating metastatic cancer to bone comprising the steps of administering an M-CSF antagonist to a subject and treating said subject with surgery or radiation therapy.

58. A method of targeting a tumor cell expressing membrane-bound M-CSF on its surface comprising the step of administering an antibody that specifically binds to the extracellular portion of membrane-bound M-CSF.

59. The method of claim 58 wherein said antibody is conjugated to a radionuclide or other toxin.

60. The method of claim 59 wherein said antibody is selected from the group consisting of:

a) a polyclonal antibody;

b) a monoclonal antibody;

c) a humanized antibody;

d) a human antibody;

e) a chimeric antibody;

f) Fab, $F(ab')_2$ or F_v antibody fragment; and

g) a mutein of any one of a) to f).

61. A method of treating a subject suffering from a cancer, wherein the cells comprising said cancer do not secrete M-CSF, comprising the step of administering an M-CSF antagonist.

62. A method of preventing bone metastases comprising administering to a

subject afflicted with metastatic cancer an amount of M-CSF antagonist effective to neutralize M-CSF produced by the subject's cells, said amount being larger than the amount effective to neutralize M-CSF produced by the cancer cells.

63. A method of treating a subject afflicted with a metastatic cancer to bone comprising administering to said subject an amount of M-CSF antagonist effective to neutralize M-CSF produced by the subject's cells, said amount being larger than the amount effective to neutralize M-CSF produced by the cancer cells.

64. The antibody of any one of claims 16-25, for use in medicine.

65. Use of a M-CSF antagonist in the manufacture of a medicament for preventing bone metastases in a subject afflicted with metastatic cancer.

66. Use of a M-CSF antagonist in the manufacture of a medicament for preventing, in a subject afflicted with metastatic cancer, bone loss associated with the cancer.

67. Use of a M-CSF antagonist in the manufacture of a medicament for treating a subject afflicted with a metastatic cancer to bone.

68. Use of a M-CSF antagonist in the manufacture of a medicament for reducing, in a subject afflicted with a metastatic cancer to bone, the severity of bone loss associated with the cancer.

69. The use according to claims 65-68 wherein said subject is a mammal.

70. The use according to claim 69 wherein said mammal is human.

71. The use according to claim 70 wherein said antagonist inhibits the interaction between M-CSF and its receptor (M-CSFR).

72. The use according to claim 71 wherein said antagonist inhibits osteoclast proliferation and/or differentiation induced by tumor cells.

73. The use according to claim 71 wherein said M-CSF antagonist is selected from the group consisting of:

a) a polypeptide comprising an anti-M-CSF antibody;

b) a polypeptide comprising an anti-M-CSFR antibody thereof;

c) a soluble polypeptide comprising an M-CSF mutein or derivative thereof; or

d) a soluble polypeptide comprising an M-CSFR mutein or derivative

thereof.

74. The use according to claim 73 wherein said antibody is selected from the group consisting of:

a) a polyclonal antibody;

b) a monoclonal antibody;

c) a humanized antibody;

d) a human antibody;

e) a chimeric antibody;

f) Fab, $F(ab')_2$ or F_v antibody fragment; and

g) a mutein of any one of a) to f).

75. The use according to claim 74 wherein the antibody is specific to M-CSF.

76. The use according to claim 75 wherein the antibody is antibody 5H4.

77. The use according to claim 74 wherein the antibody is specific to M-CSFR.

78. The use according to claim 73 wherein the metastatic cancer is breast, lung, renal, multiple myeloma, thyroid, prostate, adenocarcinoma, blood cell malignancies, including leukemia and lymphoma; head and neck cancers; gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, pancreatic cancer, liver cancer; malignancies of the female genital tract, including ovarian carcinoma, uterine endometrial cancers and cervical cancer; bladder cancer; brain cancer, including neuroblastoma; sarcoma, osteosarcoma; and skin cancer, including malignant melanoma or squamous cell cancer.

79. The use according to claims 65-68 wherein the M-CSF antagonist is an antibody administered at a dose between about 0.01 mg/kg and about 100 mg/kg.

80. Use of the antibody of any one of claims 16-25 in the manufacture of a medicament for treating a subject afflicted with metastatic cancer.

81. Use of the antibody of any one of claims 16-25 in the manufacture of a medicament for reducing, in a subject afflicted with a metastatic cancer, the severity of bone loss associated with the cancer.

82. Use of a M-CSF antagonist and a therapeutic agent in the manufacture

of a medicament for preventing, ina subject afflicted with metastatic cancer, bone metastases and tumor growth.

83. Use of a M-CSF antagonist and a therapeutic agent in the manufacture of a medicament for preventing, in a subject afflicted with metastatic cancer, bone loss associated with the cancer.

84. Use of a M-CSF anagonist and a therapeutic agent in the manufacture of a medicament for treating a metastatic cancer.

85. Use of a M-CSF antagonist and a therapeutic agent in the manufacture of a medicament for reducing the severity of bone loss associated with the cancer and inhibiting tumor growth in a subject afflicted with metstatic cancer.

86. Product comprising an M-CSF antagonist and a therapeutic agent as a combined preparation for simultaneous, separate or sequential use in treating cancer.

87. Use of an M-CSF antagonist in preparation of a medicament for preventing or treating metastatic cancer to bone, wherein the medicament is simultaneously separately or sequentially administered with a cancer therapeutic agent.

88. Use of a cancer therapeutic agent in preparation of a medicament for preventing or treating metastatic cancer to bone, wherein the medicament is simultaneously separately or sequentially administered with an M-CSF antagonist.

89. A package, vial or container comprising a medicament comprising an M-CSF antagonist and instructions that the medicament should be used in combination with surgery or radiation therapy.

90. The use according to claims 82-85 wherein said subject is a mammal.

91. The use according to claim 86 wherein said mammal is human.

92. The use according to claim 90 wherein said antagonist inhibits the interaction between M-CSF and its receptor M-CSFR.

93. The use according to claims 82-85 wherein said antagonist inhibits osteoclast proliferation and/or differentiation induced by tumor cells.

94. The use according to claim 92 wherein said M-CSF antagonist is selected from the group consisting of:

a) a polypeptide comprising an anti-M-CSF antibody;

b) a polypeptide comprising an anti-M-CSFR antibody thereof;

c) a soluble polypeptide comprising an M-CSF mutein or derivative thereof; or

d) a soluble polypeptide comprising an M-CSFR mutein or derivative thereof.

95. The use according to claim 94 wherein said antibody is selected from the group consisting of:

a) a polyclonal antibody;

b) a monoclonal antibody;

c) a humanized antibody;

d) a human antibody;

e) a chimeric antibody;

f) Fab, $F(ab')_2$ or F_v antibody fragment; and

g) a mutein of any one of a) to f).

96. The use according to claims 82-85 wherein the therapeutic agent is a bisphosphonates.

97. The use according to claim 96 wherein the bisphonate is zeledronate, pamidronate, clodronate, etidronate, tilundronate, alendronate, or ibandronate.

98. The use according to claims 82-85 wherin the therapeutic agent is a chemotherapeutic agent.

99. The use according to claim 51 wherein the subject is precluded from receiving bisphophonate treatment.

100. Use of a M-CSf antagonist in the manufacture of a medicament for reducing the dose of a therapeutic agent administered to a subject to treat or prevent bone metastases and tumor growth.

101. Use of a M-CSF antagonist, a therapeutic agent, and a non-M-CSF colony stimulating factor in the manufacture of a medicament for preventing, in a subject afflicted with metastatic cancer, bone metastases and tumor growth.

102. Use of a M-CSF antagonist, a therapeutic agent, and a non-M-CSF colony stimulating factor in the manufacture of a medicament for preventing, in a subject

afflicted with metastatic cancer,bone loss associated with the cancer.

103. Use of a M-CSF antagonist, a therapeutic agent, and a non-M-CSF colony stimulating factor in the manufacture of a medicament for treating a metastatic cancer.

104. Use of a M-CSF antagonist, a therapeutic agent, and a non-M-CSF colony stimulating factor in the manufacture of a medicament for reducing the severity of bone loss associated with the cancer and inhibiting tumor growth in a subject afflicted with metastatic cancer.

105. The use according to any one of claims 101-103 wherein the non-M-CSF colony stimulating factor is G-CSF.

106. Use of am antibody that specifically binds to the extracellular portion of membrane-bound M-CSF in the manufacture of a medicament for targeting a tumor cell that expresses membrane-bound M-CSf on its surface.

107. Use of an antibody that (a) specifically binds to the extracellula portion of membrane-bound M-CSF, and (b) is conjugated to a radionuclide or other toxin in the manufacture of a medicament for treating cancer.

108. The use of claim 107 wherein said antibody is selected from the group consisting of:

a) a polyclonal antibody;

b) a monoclonal antibody;

c) a humanized antibody;

d) a human antibody;

e) a chimeric antibody;

f) Fab, $F(ab')_2$ or F_v antibody fragment; and

g) a mutein of any one of a) to f).

109. Use of a non-murine anti-M-CSF antibody in the manufacture of a medicament for treating cancer.

110. The use according to claim 109 wherein the cells comprising the cancer do not secrete M-CSF.

111. Use of a M-CSF antagonist, in an amount that is larger that the amount effective to neutralize M-CSF produced by cancer cells, in the manufacture of a medicament

for preventing bone metastases.

112. Use of a M-CSF antagonist, in an amount that is larger that the amount effective to neutralize M-CSF produced by cancer cells, in the manufacture of a medicament for neutralizing M-CSF produced by a subject's cells.

113. Use of a M-CSF antagonist, in an amount that is larger that the amount effective to neutralize M-CSF produced by cancer cells, in the manufacture of a medicament for treating a subject afflicted with a metastatic cancer to bone.

114. Use of a M-CSF antagonist, in an amount that is larger that the amount effective to neutralize M-CSF produced by cancer cells, in the manufacture of a medicament for treating cancer.